Pre-orchiectomy tumor marker levels should not be used for International Germ Cell Consensus Classification (IGCCCG) risk group assignment

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Abstract: PURPOSE To investigate whether the use of pre-orchiectomy instead of pre-chemotherapy tumor marker (TM) levels has an impact on the International Germ Cell Consensus Classification (IGCCCG) risk group assignment in patients with metastatic germ cell tumors (GCT). METHODS Demographic and clinical information of all patients treated for primary metastatic testicular non-seminomatous GCT in our tertiary care academic center were extracted from medical charts. IGCCCG risk group assignment was correctly performed with pre-chemotherapy marker levels and additionally with pre-orchiectomy marker levels. Agreement between pre-chemotherapy and pre-orchiectomy risk group assignments was assessed using Cohen's kappa. RESULTS Our cohort consisted of 83 patients. The use of pre-orchiectomy TMs resulted in an IGCCCG risk group upstaging in 12 patients (16%, 8 patients from good to intermediate risk and 4 patients from intermediate to poor risk) and a downstaging in 1 patient (1.2%, from intermediate- to good-risk). The agreement between pre-orchiectomy and pre-chemotherapy IGCCCG risk groups resulted in a Cohen's kappa of 0.888 ($p < 0.001$). CONCLUSIONS Using pre-orchiectomy TMs can result in incorrect IGCCCG risk group assignment, which in turn can impact on the clinical management and follow-up of patients with metastatic GCT. Thus, adherence to the IGCCCG standard using pre-chemotherapy TMs levels is recommended.

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Pre-orchiectomy tumor marker levels should not be used for International Germ Cell Consensus Classification (IGCCCG) risk group assignment

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Abstract

Purpose To investigate whether the use of pre-orchiectomy instead of pre-chemotherapy tumor marker (TM) levels has an impact on the International Germ Cell Consensus Classification (IGCCCG) risk group assignment in patients with metastatic germ cell tumors (GCT).

Methods Demographic and clinical information of all patients treated for primary metastatic testicular non-seminomatous GCT in our tertiary care academic center were extracted from medical charts. IGCCCG risk group assignment was correctly performed with pre-chemotherapy marker levels and additionally with pre-orchiectomy marker levels. Agreement between pre-chemotherapy and pre-orchiectomy risk group assignments was assessed using Cohen's kappa.

Results Our cohort consisted of 83 patients. The use of pre-orchiectomy TMs resulted in an IGCCCG risk group upstaging in 12 patients (16%, 8 patients from good- to intermediate-risk and 4 patients from intermediate- to poor-risk) and a downstaging in 1 patient (1.2%, from intermediate- to good-risk). The agreement between pre-orchiectomy and pre-chemotherapy IGCCCG risk groups resulted in a Cohen's kappa of 0.888 ($p<0.001$).

Conclusions Using pre-orchiectomy TMs can result in incorrect IGCCCG risk group assignment, which in turn can impact on the clinical management and follow-up of patients with metastatic GCT. Thus, adherence to the IGCCCCG standard using pre-chemotherapy TMs levels is recommended.

Keywords: testicular germ cell tumor; Biomarkers, Tumor; prognosis

Introduction

One third of all patients presenting with testicular germ cell tumors (GCT) have metastases at initial diagnosis (DeSantis et al. 2014). An additional 15 - 30% of patients with initially localised disease will develop metastatic disease during follow-up (Chung et al. 2015; Daugaard et al. 2014). In 1997, the International Germ Cell Cancer Cooperative Group (IGCCCG) published a prognostic classification system, which is based on the histological subtype

(seminoma vs. non-seminoma), the location of the primary tumor, the extent of metastatic spread as well as the level of the pre-chemotherapy tumor markers (TM) alpha-fetoprotein (AFP), human chorionic gonadotropin (bHCG) and lactate dehydrogenase (LDH) (International-Germ-Cell-Cancer-Collaborative-Group 1997). In clinical practice, the IGCCCG risk group assignment is sometimes incorrectly performed by using pre-orchiectomy instead of pre-chemotherapy TM levels. This mistake may have impact on the treatment and follow-up intensity and thus, on the oncological outcome.

The aim of our investigation was to assess whether the use of pre-orchiectomy instead of pre-chemotherapy TM levels has an impact on the IGCCCG risk group assignment and thus intensity of treatment in patients with metastatic testicular GCT.

Patients and methods

We identified patients who underwent first-line chemotherapy for primary metastatic non-seminomatous GCT of the testis in our institution between 1991 and 2015. Patients with extragonadal GCTs, bilateral testicular GCTs or missing follow-up information were excluded from our analysis. Pre-chemotherapy baseline characteristics (age, histology of the primary tumor, site and extent of metastases) and pre-orchiectomy and pre-chemotherapy TM levels were retrieved from electronic medical records as both assessments are clinical routine at our center.

IGCCCG risk group assignment was correctly performed with pre-chemotherapy TM levels and compared to the incorrect one based on pre-orchiectomy TM levels. Agreement between pre-chemotherapy and pre-orchiectomy IGCCCG risk group assignments was assessed using Cohen's kappa. An kappa of 0.61-0.8 was interpreted as substantial and 0.81-1.00 as an excellent agreement (Landis and Koch 1977).

Statistical analyses were performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, New York, USA). The results for continuous normally distributed variables are expressed as mean ± standard deviation (SD). Continuous non-normally distributed variables are presented as median and interquartile ranges (IQR) and categorical variables are presented as number and percent. All p-values <0.05 were considered statistically significant. All statistical tests were two-sided. The local ethics committee approved the study protocol (STV KEK-ZH 25-2008).

Results

A total of 83 patients with primary metastatic testicular non-seminomatous GCTs were identified. Their baseline characteristics are summarized in Table 1. TM levels changed after orchiectomy as follows: AFP decreased by a median of 5µg/l (IQR 0 to 108 µg/l), bHCG decreased with a median change of 0 U/l (IQR -5 to 235 U/l), and LDH decreased by a median of 82U/l (IQR 0-158 U/l). After orchiectomy AFP changed over 1000 µg/l in 11 patients, but only 5 patients had an AFP induced IGCCCG reclassification because patients were already classified as intermediate or poor risk (Figure 1 & Table 2). Similarly 14 patients had bHCG changes over 5000 U/l after orchiectomy but IGCCCG reclassification was observed in only 6 patients because of the same reason. Significant changes of LDH levels >720 U/l were observed in 6 patients but incorrect upstaging from good to intermediate risk was documented in only 3 patients.

Fifty men (60%) were assigned to the IGCCCG good-risk group, 19 (23%) to the intermediate-risk group, and 14 (17%) to the poor-risk group (Table 3). When pre-orchiectomy instead pre-chemotherapy TM levels were used for IGCCCG risk group assignment, 43 patients (52%) were assigned to the good-risk group, 22 (27%) to the intermediate-risk group and 18 (21%) to the poor risk group. Pre-orchiectomy TMs resulted in an IGCCCG risk group change in 13 patients (16%). Eight (10%) patients changed from good to intermediate risk and four (5%) patients from intermediate to poor-risk. One patient (1%) showed quickly rising AFP levels after orchiectomy. Using pre-orchiectomy TM levels would have led to an assignment to the good instead of intermediate-risk group. The overall agreement between pre-chemotherapy and pre-orchiectomy IGCCCG risk groups assignment was excellent with a Cohen's kappa of 0.888 ($p<0.001$).

Discussion

Our analysis revealed that the use of pre-orchiectomy TM levels frequently results in an upgrade and less frequently in a downgrade of the IGCCCG risk group assignment and thus can lead to incorrect treatmentss and unnecessary follow-up investigations.

Given that cancer cells in the affected testis represent a relevant source of TM production, the burden of metastastic disease is better represented by the pre-chemotherapy TMs after removal of the primary tumor. In our cohort pre-orchiectomy TM levels led to an upstaging from good to intermediate risk in 10% and from intermediate to poor risk in 5% of all patients. Given the fact that the IGCCCG classification is also used to determine the intensity of subsequent chemotherapy (i.e. 3 cycles for good risk and 4 cycles for intermediate and poor risk) incorrect classification may lead to overtreatment, which would result into unnecessary toxicity (Chovanec et al. 2017; Kerns et al. 2018) without an oncological benefit. Furthermore, incorrect upstaging may also trigger more intense follow-up investigations (e.g. more office visits, TM analyses and potentially harmful CT scans). On the other hand, one patient with rapidly rising AFP levels post-orchiectomy would have been incorrectly downstaged by pre-orchiectomy TM levels. Although our results indicated that only a minority of patients might be affected, incorrect IGCCCG risk group assignment may have also devastating consequences from undertreatment in individual patients.

In conclusion, IGCCCG risk group assignment should be performed carefully to avoid misclassification that can result in over- and undertreatment. Based on our results we suggest to exclusively assign IGCCCG risk groups based on pre-chemotherapy TM levels.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent: informed consent was waived by the local ethic committee (STV KEK-ZH 25-2008).

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Conflict of interest

The authors declare no conflict of interest.

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None

Table 1 Baseline characteristics

	N = 83
Age (years) (±SD)	30 (±9)
IGCCCG risk groups - Good risk n (%) - Intermediate risk n (%) - Poor risk n (%)	 50/83 (60%) 19/83 (23%) 4/83 (17%)
Site of metastases - Retroperitoneal lymph nodes - Lung - Mediastinal - Neck - Liver - Bone - Brain - Other	 74/83 (89%) 47/83 (57%) 20/83 (24%) 8/83 (10%) 5/83 (6%) 4/83 (5%) 2/83 (2%) 4/83 (5%)
Pre- chemotherapy tumor markers levels **AFP** (µg/l)[IQR] **bHCG** (U/l) [IQR] **LDH** (U/l)[IQR]	 53.7 [3.8 – 627.0] 51.0 [0.0 – 2862.0] 387 [450 – 720]

AFP= Alpha-fetoprotein, bHCG=Beta-human chorionic gonadotropin, LDH=Lactate dehydrogenase, SD=Standard deviation

Table 1 Baseline characteristics

	N = 83
Age (years) (±SD)	30 (±9)
IGCCCG risk groups	
- Good risk n (%)	50 (60%)
- Intermediate risk n (%)	19 (23%)
- Poor risk n (%)	4 (17%)
Site of metastases	
- Retroperitoneal lymph nodes	74 (89%)
- Lung	47 (57%)
- Mediastinal	20 (24%)
- Neck	8 (10%)
- Liver	5 (6%)
- Bone	4 (5%)
- Brain	2 (2%)
- Other	4 (5%)
Pre-chemotherapy tumor markers levels	
AFP (µg/l)[IQR]	53.7 [3.8 – 627.0]
bHCG (U/l) [IQR]	51.0 [0.0 – 2862.0]
LDH (U/l)[IQR]	387 [450 – 720]

AFP= Alpha-fetoprotein, bHCG=Beta-human chorionic gonadotropin, IQR= interquartile range, LDH=Lactate dehydrogenase, SD=Standard deviation

Table 2 Tumor marker change scores and reasons of patients with upstaging or downstaging of IGCCCG assignments

				AFP			bHCG			LDH		
Correct IGCCCG	**Incorrect pre-orchiectomy IGCCCG**	**Change in IGCCCG assignment**	**Reason for upstaging**	**pre orchiectomy (µg/l)**	**pre chemotherapy (µg/l)**	**change (µg/l)**	**pre orchiectomy (U/l)**	**pre chemotherapy (U/l)**	**change (U/l)**	**pre orchiectomy (U/l)**	**pre chemotherapy (U/l)**	**change (U/l)**
Good	Intermediate	Upstaging	AFP, HCG	1009.4	3.1	1006.3	1249.9	0	1249.9	524	518	6
Good	Intermediate	Upstaging	AFP	2294.9	567.5	1727.4	9.5	7.2	2.3	411	386	25
Good	Intermediate	Upstaging	AFP	4905	774.6	4130.4	13.5	0	13.5	700	445	255
Good	Intermediate	Upstaging	HCG	1.8	1.7	0.1	12528	3456	9072	442	329	113
Good	Intermediate	Upstaging	HCG	499	60.4	438.6	37401	2927	34474	432	377	55
Intermediate	Poor	Upstaging	AFP	31800	2760	29040	6995	3367	3628	553	438	115
Intermediate	Poor	Upstaging	HCG	5	3	2	65523	24313	41210	364	291	73
Intermediate	Poor	Upstaging	HCG	1.9	2.7	-0.8	71885	29696	42189	610	336	274
Intermediate	Poor	Upstaging	HCG	7	4.5	2.5	81326	9917.5	71408.5	314	179	135
Good	Intermediate	Upstaging	LDH	9.3	4.99	4.31	13.7	NA	NA	3258	387	2871
Good	Intermediate	Upstaging	LDH	53.7	30.8	22.9	24	7.8	16.2	1094	466	628
Good	Intermediate	Upstaging	LDH	4.8	3.8	1	4	0	4	795	685	110
Intermediate	Good	Downstaging	AFP	529	1804	-1275	94	207	-113	172	303	-131

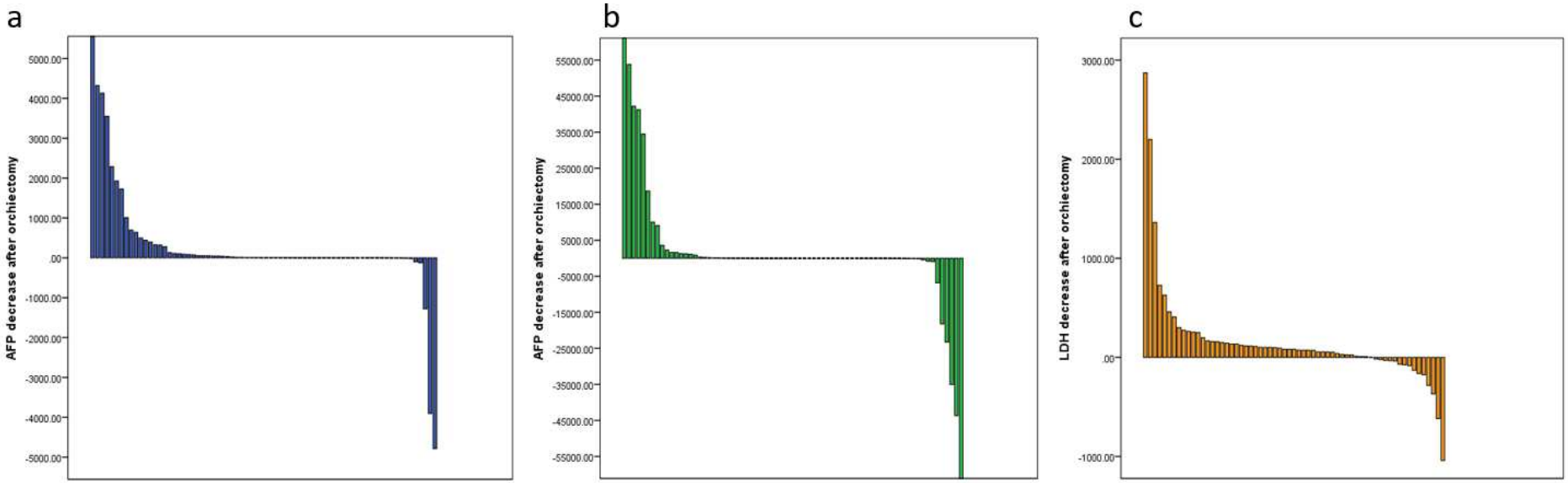
AFP= Alpha-fetoprotein, bHCG=Beta-human chorionic gonadotropin, LDH=Lactate dehydrogenase (upper level of normal is 480 U/l)

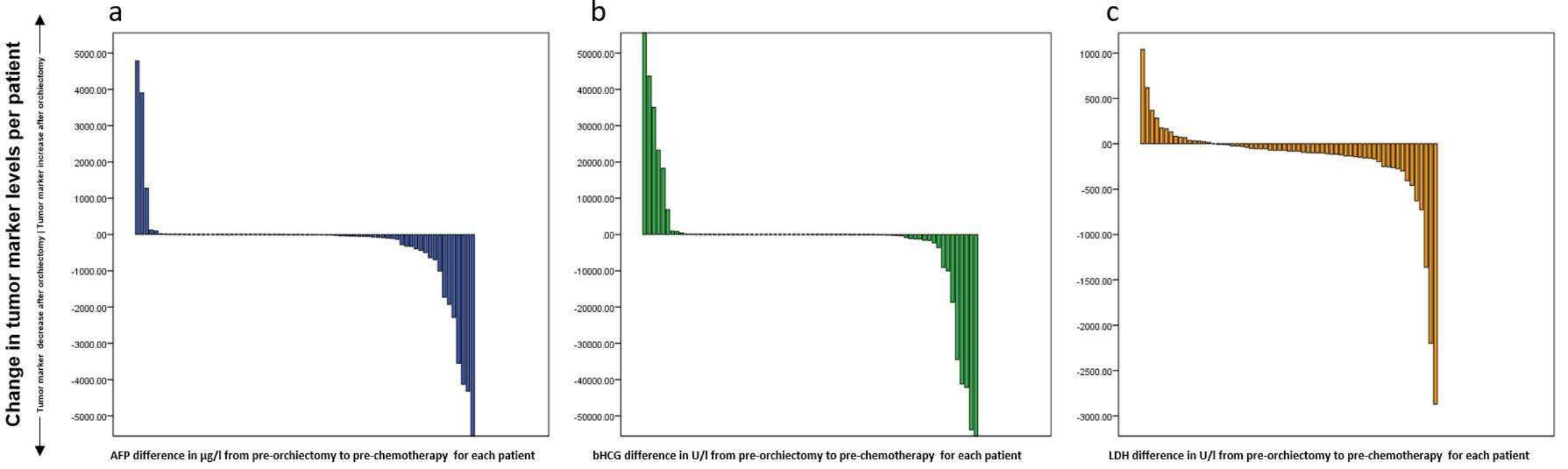
Table 3 International Germ Cell Cancer Collaborative Group (IGCCCG) risk group assignment using either preorchiectomy (columns) or prechemotherapy (rows) tumor marker levels. Highlighted cells in green indicate no change, in red upstaging and in magenta downstaging in IGCCCG assignments

		Preorchiectomy			
		Good risk	**Intermediate**	**Poor risk**	
Prechemotherap	Good risk	42	8	0	50
	Intermediate risk	1	14	4	19
	Poor risk	0	0	14	14
		43	22	18	83

Color legend
No change
Upstaging
Downstaging

Figure 1 Waterfall plots of tumor marker decrease after orchiectomy for APF (a), HCG (b) and LDH (c)




a
b
c
Change in tumor marker levels per patient
Tumor marker decrease after orchiectomy | Tumor marker increase after orchiectomy
5000.00
4000.00
3000.00
2000.00
1000.00
.00
-1000.00
-2000.00
-3000.00
-4000.00
-5000.00
50000.00
40000.00
30000.00
20000.00
10000.00
.00
-10000.00
-20000.00
-30000.00
-40000.00
-50000.00
1000.00
500.00
.00
-500.00
-1000.00
-1500.00
-2000.00
-2500.00
-3000.00
AFP difference in µg/l from pre-orchiectomy to pre-chemotherapy for each patient
bHCG difference in U/l from pre-orchiectomy to pre-chemotherapy for each patient
LDH difference in U/l from pre-orchiectomy to pre-chemotherapy for each patient